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Brain areas associated with force steadiness and intensity during isometric ankle dorsiflexion in men and women

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Abstract

Although maintenance of steady contractions is required for many daily tasks, there is little understanding of brain areas that modulate lower limb force accuracy. Functional magnetic resonance imaging was used to determine brain areas associated with steadiness and force during static (isometric) lower limb target-matching contractions at low and high intensities. Fourteen young adults (6 men and 8 women; 27.1 ± 9.1 years) performed three sets of 16-s isometric contractions with the ankle dorsiflexor muscles at 10, 30, 50, and 70 % of maximal voluntary contraction (MVC). Percent signal changes (PSCs, %) of the blood oxygenation level-dependent response were extracted for each contraction using region of interest analysis. Mean PSC increased with contraction intensity in the contralateral primary motor area (M1), supplementary motor area, putamen, pallidum, cingulate cortex, and ipsilateral cerebellum ($p < 0.05$). The amplitude of force fluctuations (standard deviation, SD) increased from 10 to 70 % MVC but relative to the mean force (coefficient of variation, CV %) was greatest at 10 % MVC. The CV of force was associated with PSC in the ipsilateral parietal lobule ($r = -0.28$), putamen ($r = -0.29$), insula ($r = -0.33$), and contralateral superior frontal gyrus ($r = -0.33$, $p < 0.05$). There were minimal sex differences in brain activation across the isometric motor tasks indicating men and women were similarly motivated and able to activate cortical motor centers during static tasks.

Control of steady lower limb contractions involves cortical and subcortical motor areas in both men and women and provides insight into key areas for potential cortical plasticity with impaired or enhanced leg function.

Keywords

Functional magnetic resonance imaging (fMRI); Isometric contraction; Lower limb muscles; Force fluctuations; Sex differences

Introduction

Steady postural contractions that stabilize a limb with accuracy are required for successful performance of many daily tasks including carrying objects, driving, and walking. Stabilizing contractions across a range of intensities require appropriate neural activity in cortical centers. Early work in monkeys established the central role of discharge rates of primary motor cortex (M1) cells during graded voluntary movements of distal upper limb muscles (Evarts 1968). Subsequent development of imaging techniques in humans including functional magnetic resonance imaging (fMRI) has established positive associations between contraction force intensity of the upper limb and cortical activation indicated by the blood oxygenation level dependent (BOLD) response (e.g., Thickbroom et al. 1998; Spraker et al. 2007; van Duinen et al. 2008; Keisker et al. 2009). However, there remains uncertainty as to the role of intensity and volume of cortical activation in force regulation (Dai et al. 2001) and the motor areas involved with increased activation especially among lower-to-moderate force contractions, which are forces at which many daily tasks are performed (Spraker et al. 2007; van Duinen et al. 2008; Keisker et al. 2009).

Despite the primary role of lower limb muscles as agonists and stabilizers during functional tasks such as driving and walking, most studies have studied upper limb muscles and little is understood about cortical activation during leg movements. Understanding key cortical areas associated with control of the lower leg in healthy young adults establishes a foundation for identifying the plasticity of these areas with impaired motor function that can occur with aging and neurological conditions as well as enhanced function that is possible with physical exercise in all populations. Some studies have determined areas of activation during foot exercise (e.g., MacIntosh et al. 2004; Ciccarelli et al. 2005; Huda et al. 2008), but the relation between activation and force intensity has not been systematically determined. For lower limb muscles, activation strategies within the cortex (shown as the intensity of the BOLD signal and volume of activation) may differ to that of the more commonly studied hand muscles: the lower limb muscles have a reduced need for fine motor control compared with hand muscles, they have a larger muscle mass and motor unit ratio (Feinstein et al. 1955), and fewer direct corticospinal connections (Brouwer and Ashby 1990) compared with upper limb muscles. Further, the tibialis anterior has a greater motor unit recruitment range than, for example, the first dorsal interosseous (De Luca et al. 1982; Van Cutsem et al. 1997; Moritz et al. 2005). Therefore, a purpose of this study was to determine force-related changes across a range of low and high forces in the BOLD signal (intensity and volume) of cortical regions during isometric ankle dorsiflexion contractions in healthy young adults.

Because the rate of movement during dynamic or brief repetitive isometric contraction mode can affect the BOLD signal (Rao et al. 1996), we used sustained isometric contractions between 10 and 70 % of maximal strength. We hypothesized that motor areas of the brain would scale linearly with an increase in force intensity of the ankle dorsiflexor muscles.

When sustaining a postural static contraction as is often required during standing, the force exerted to maintain the isometric contraction fluctuates around a mean target force and is often referred to as steadiness (Enoka et al. 2003). The amplitude of the force fluctuations (standard deviation (SD) of the force) increases with force intensity due to activation of more motor units. When the standard deviation is normalized to the mean force (coefficient of variation, CV), the force fluctuations do not increase with intensity and are usually larger at lower intensities of contraction (e.g., Taylor et al. 2003; Moritz et al. 2005; Tracy et al. 2007; Jesunathadas et al. 2012). CV of force is mediated primarily by low-frequency oscillations in neural drive (<2–3 Hz) seen as the oscillations of the trains of motor unit action potentials (Negro et al. 2009; Dideriksen et al. 2012), with a greater influence of synaptic noise and motor unit discharge rate variability at low forces (Jesunathadas et al. 2012). The low-frequency oscillating neural drive reflects an integration of both descending and afferent inputs (Negro et al. 2009; Dideriksen et al. 2012; Farina et al. 2012). A novel aspect of this study was to identify and understand those cortical areas that are related to the force fluctuations across a range of forces in young adults. We hypothesized that at lower intensities of contraction, larger fluctuations in force (CV) would be associated with greater activation of cortical motor areas.

Both men and women were tested, so we also determined whether there were any sex differences that could be detected in brain activity and modulation of the low-and high-force isometric contractions with the lower limb. Sex differences have been shown in brain activity during cognitive tasks of equal performance in men and women, such that women have greater brain activation for the same task (Wang et al. 2007) and some differences during finger tapping (Lissek et al. 2007). Whether there are sex differences in brain activation during motor tasks with the lower limb has not been assessed. Various indirect measures of motor unit activity (electromyography, EMG) and assessments of voluntary activation (e.g., techniques of stimulation along the neuroaxis to determine neural drive to the muscle and to the motor cortex) indicate no sex difference in the output of activation from the motor cortex (Hunter and Enoka 2001; Hunter et al. 2006; Keller et al. 2011). We hypothesized therefore, that men and women would have similar PSC during graded and controlled static contractions.

Methods

Participants

Fourteen healthy young adults (6 men and 8 women; mean \pm SD; 27.1 ± 9.1 years, 170.5 ± 9.5 cm in height, 66.5 ± 11.2 kg in body mass) volunteered to participate in the study. All participants were healthy with no known neurological or cardiovascular diseases and were naive to the protocol. Each participant provided informed consent, and the protocol was approved by the institutional review boards at Marquette University and Medical College of

Wisconsin. Participants reported to the laboratory once for a familiarization session and then for an experimental session in the MRI scanner.

Setup and mechanical recordings

Participants laid supine in a 3.0 Tesla short bore MRI Scanner (General Electric Healthcare, Waukesha, WI) with the hip and knee at 45° of flexion (full extension is 0°). The right foot was assessed with the ankle in a neutral position (0° dorsiflexion). During the static (isometric) voluntary contractions, force of the ankle dorsiflexor muscles was measured with a force transducer (Transducer Techniques, Temecula, CA) mounted at a right angle under a footplate that was adjustable for angle and was rigidly secured to the distal end of the scanner bed (polycarbonate platform). The forefoot was secured to the footplate via a strap placed 1–2 cm proximal to the metatarsophalangeal joint of the toes. The forces detected by the transducer were recorded online at 500 samples/s with a Power 1401 A/D converter and Spike2 software (Cambridge Electronics Design, Cambridge, UK). The force signal was displayed via a rear-projection visual display system for participant feedback. During the submaximal contraction, the visual display feedback was adjusted for each participant using their maximal strength value. A horizontal cursor representing the baseline was displayed at 12.5 % of the height of the screen, and a horizontal cursor representing the required target force was displayed at 75 % of the height of the screen. The force output was displayed at a refresh rate of 60 Hz and a resolution of 800 × 600 pixels. Each participant was asked to trace the horizontal cursor with the force signal as steadily and accurately as possible.

Experimental protocol

Once the participant was setup in the fMRI environment, they performed at least three maximal voluntary contractions (MVC) for 3- to 5-s duration to obtain maximal strength (Fig. 1). If peak forces from two of the three trials were not within 5 % of each other, additional trials were performed until this was accomplished. The greatest force achieved by the subject was taken as the MVC and used as the reference to calculate the target force. Each participant performed three sets (runs) of isometric contractions at 10, 30, 50, and 70 % of MVC in a randomized order. Each contraction was held for 16 s followed by 60-s rest to avoid fatigue. Participants received real-time force feedback during the contraction via a rear-projection visual display system and were required to track a horizontal target line on the display screen.

MRI acquisition

Magnetic resonance images were collected in General Electric Signa Excite 3.0 Tesla short bore MR Scanner (GE Healthcare, Waukesha, WI). Functional MRI was used to quantify the BOLD contrast (T2*-weighted imaging) overlaid on a T1-weighted anatomical image for each subject. An 8-channel array radio frequency receive head coil (GE Healthcare, Waukesha, WI) was used to obtain 36 sagittal plane slices (thickness = 4 mm) across the entire brain volume using an echo-planar imaging sequence (64 × 64 matrix, 240 × 240 mm² field of view, TE = 25 ms, TR = 2,000 ms, and flip angle = 77°). Voxel size was 3.75 × 3.75 × 4 mm. Immediately after completion of the protocol, 148 high-resolution spoiled GRASS (gradient recalled at steady state) anatomical images (thickness = 1 mm) were collected (256 × 244 matrix, TE = 3.9 ms, TR = 9.5 ms, and flip angle = 12°).

Data analysis

Mechanical data analysis—The torque for each MVC and submaximal contractions was calculated as the product of force and the distance between the ankle joint and the point at which the foot attached to the middle of the strap on the force transducer. The MVC torque was quantified as the average value over a 0.5-s interval that was centered about the peak. The fluctuations in torque for each 16-s contraction were quantified in two ways: (1) the standard deviation (SD) of the torque, and (2) the coefficient of variation ($CV = SD/mean \times 100\%$) which normalized the absolute amplitude of the fluctuations to the mean torque exerted during each contraction.

fMRI data analysis—The public domain software, analysis of functional neuroimages (AFNI, <http://afni.nimh.nih.gov/afni/>), was used to analyze the fMRI data sets. For each participant, all acquired functional 2D images from the scanner were converted to AFNI format and were aligned with slice timing correction. The time series of functional image volumes were spatially realigned to correct the effect of head motion. General linear modeling [3dDeconolve, AFNI (Cox 1996)] was used to regress a model of the contraction and rest blocks with the BOLD data. All contraction blocks (total 12 contractions = 4 intensities \times 3 trials) were used for the model to calculate the regression coefficient of each voxel and then used to create a task-related activation map. In addition, 3 contraction blocks at each intensity condition were also used for the model to create a task-related activation map at each contraction intensity separately (Fig. 3). Separate amplitudes were computed for each of the four contraction intensities. These amplitudes were warped to Talairach (Talairach and Tournoux 1988) space and blurred (4 mm FWHM Gaussian) and then were used as the percent signal change (PSC, %). The group analysis was performed for contraction versus rest (3dttest). The results were thresholded using AlphaSim (whole brain corrected $p = 0.05$, cluster size = 168 ul) to create a task-related activation map. This map was used as a mask for regions of interest (ROI) analysis later. The percent signal change was extracted for each contraction intensity for each subject. Repeated-measures ANOVAs were performed to test for differences across force levels (10, 30, 50, and 70 % of MVC: force effect) in the BOLD PSC of each activated area.

To compare the activation volume in each anatomical area separately within the whole brain, we used the CA N27 macrolevel map in the AFNI toolbox as a mask rather than a task-related activation map. A total of 116 ROI masks were overlapped with PSC amplitude data for the 4 different torque intensities. Data were thresholded with the average value of all PSC calculated from ROI analysis. The volume in each area that showed a higher signal change than the threshold was used as the activation volume. Repeated-measures ANOVAs were performed to test the force effect on the activation volume of each of the 116 regions. One participant was excluded from the study due to severe motion artifact (>2 mm).

Statistical analysis

Data are reported as means \pm SD within the text and displayed as means \pm SE in the figures. Three-way ANOVAs (sex as a fixed factor) with repeated measures on individual run (1, 2, and 3) and force levels (10, 30, 50, and 70 % of MVC) were used to test for between- and within-group differences in average torque and torque fluctuations. Two-way ANOVAs (sex

as a fixed factor) with repeated measures on intensity of torque (10, 30, 50, and 70 % of MVC) were used to test for between- and within-group differences in percent signal change and activation volume. When the significant main effect of the force level was found, a contrast option was used to compare between each intensity of torque (10, 30, 50, and 70 % of MVC) and the trends (linear, quadratic, and cubic) were also determined using the tests of within-subject contrasts table. When a significant sex-related interaction and main effect of sex were found, preplanned t tests were performed at each intensity to find the sex difference. Pearson product-moment correlations were used to determine the relationships between the force fluctuation and the PSCs of BOLD response in a selected area. We further examined trends in the percent signal change with increased intensity of force (e.g., logarithmic and sigmoidal trends) using the curve estimation function in SPSS program as others have done (Cheney and Fetz 1980; Dettmers et al. 1996; Ashe 1997). A significance level of $p < 0.05$ was used to identify statistical significance.

Results

Head movement

Maximal head displacements were 0.54 ± 0.5 , 0.27 ± 0.1 , and 1.37 ± 1.25 mm for anterior–posterior, right–left, and inferior–superior directions, respectively. One participant was excluded due to excessive head motion.

Torque (force) and steadiness

Torque—Maximal voluntary contraction torque of the ankle dorsi-flexors was 31.4 ± 6.8 Nm (range 21.0 to 43.9 Nm). For the submaximal target contractions, there was no difference in torque between the three runs [$F(2, 26) = 0.49$, $p = 0.62$] so the three runs were averaged for each intensity of torque (Fig. 2a). Average torque was significantly different between each target torque intensity [main effect of force, $F(3, 10) = 81.4$, $p < 0.001$]. Men were stronger than women [men vs. women; 35.7 ± 6.2 vs. 28.2 ± 6.1 Nm, $t(12) = 2.29$, $p = 0.041$], but when normalized to the absolute MVC, they performed the contractions at similar intensities.

Torque fluctuations (steadiness)—The SD of torque did not differ between the three runs [$F(2, 26) = 1.65$, $p = 0.21$] so the SD values from the three runs were averaged for each intensity of torque. The SD of torque increased with intensity of contraction from 10 to 70 % of MVC [main effect of torque intensity, $F(3, 11) = 42.0$, $p < 0.001$] in a linear [$F(1, 13) = 90.4$, $p < 0.001$] and quadratic trend [$F(1, 13) = 12.6$, $p = 0.004$] (Fig. 2b). There was no difference in SD of torques between men and women [sex effect, $F(1, 12) = 0.52$, $p = 0.48$] across contraction intensities [sex \times intensity interaction, $F(3, 36) = 0.03$, $p = 0.99$].

To determine the CV, the amplitude of torque fluctuations (SD) was normalized to the mean torque exerted for each contraction intensity, for each participant. There was no difference in the CV (%) between the runs [$F(2, 12) = 0.83$, $p = 0.46$] so the CV values from the three runs were averaged for each intensity of torque (Fig. 2c). CV of torque differed between intensities [main effect of torque intensity, $F(3, 11) = 32.7$, $p < 0.001$] because the CV at the 10 % MVC was greater than the other forces and with difference between 30 and 70 %

MVC. Thus, the CV decreased with intensity of force and best described as a quadratic trend [$F(1, 13) = 83.0, p < 0.001$] (Fig. 2c). There was no difference in CV of torques between men and women [sex effect, $F(1, 12) = 1.37, p = 0.27$] across contraction intensities [sex \times intensity interaction, $F(3, 10) = 0.36, p = 0.78$].

Brain activation areas

Regions of interest were generated and indicated that both cortical and subcortical regions were significantly activated during right ankle isometric dorsiflexion (see Table 1 and Fig. 3).

ROI analysis using activation map

Percent signal change (intensity of BOLD response) and torque

Left putamen—There was a main effect of torque intensity for the mean PSC [$F(3, 39) = 3.38, p = 0.028$]. The PSC increased linearly with greater contraction intensity [$F(1, 13) = 5.89, p = 0.030$] so that the PSC of the 70 % MVC was greater than the 10 % MVC ($p = 0.036$). The PSC also showed logarithmic and sigmoidal increases as the torque increases (logarithmic and sigmoidal; $p = 0.041$ and 0.048 , respectively). See Fig. 4a.

Right cerebellum (III)—There was a main effect of torque intensity for the PSC [$F(3, 11) = 4.56, p = 0.026$]. The PSC increased linearly as contraction intensity increased [$F(1, 13) = 12.4, p = 0.004$] so that PSC for the 50 and 70 % MVC was greater than during the 10 % MVC ($p = 0.032$ and $p = 0.003$, respectively). The PSC also showed logarithmic and sigmoidal increases as the torque increases (logarithmic and sigmoidal; $p = 0.001$ and $p < 0.001$, respectively). See Fig. 4b.

Left paracentral lobule/SMA—There was a main effect of torque intensity for the mean PSC [$F(3, 39) = 6.28, p = 0.001$]. PSC increased linearly with the increase in contraction intensity [$F(1, 13) = 9.08, p = 0.010$] so that the PSC for the 50 and 70 % MVC was greater than for the 10 % MVC ($p = 0.022$ and $p = 0.011$, respectively). The PSC also showed logarithmic and sigmoidal increases as the torque increases (logarithmic and sigmoidal; $p = 0.045$ and 0.037 , respectively). See Fig. 4c.

Left middle cingulate cortex—There was a main effect of torque intensity for the PSC [$F(3, 39) = 4.34, p = 0.010$]. PSC increased linearly with increased contraction intensity [$F(1, 13) = 6.43, p = 0.025$] so that the PSC for the 70 % MVC was greater than for the 10 and 30 % MVC ($p = 0.040, 0.013$, respectively). The PSC also showed logarithmic and sigmoidal increases as the torque increases (logarithmic and sigmoidal; $p = 0.018$ and 0.011 , respectively). See Fig. 4d.

Left pallidum—There was a main effect of torque intensity for the mean PSC [$F(3, 11) = 8.00, p < 0.001$]. The PSC increased linearly with increased contraction intensity [$F(1, 13) = 34.4, p < 0.001$] so that the PSC for the 70 % MVC was greater than all the other conditions ($p = 0.001$ to 0.035). PSC for the 50 % MVC was also greater than during the 10 % MVC ($p = 0.049$). The PSC also showed logarithmic and sigmoidal increases as the torque increases (logarithmic and sigmoidal; $p = 0.002$ and 0.008 , respectively). See Fig 4e.

Sex differences in activation

There were no sex differences in intensity of activation (PSC) in the activated areas tested except in the right inferior temporal gyrus where men showed a greater PSC than women during the 70 % MVC [0.65 ± 0.25 vs. 0.32 ± 0.21 , respectively; $t(12) = 2.623$, $p = 0.022$].

Activation volume (voxel number)

Several regions showed activation of additional voxels as force increased from low to high intensities of contraction (see Table 2). These areas are detailed below.

Right inferior frontal gyrus (p. Orbitalis)—Activation volumes were $3,928 \pm 1,544$, $3,077 \pm 2,010$, $4,663 \pm 1,973$, and $5,091 \pm 1,930$ voxels at 10, 30, 50, and 70 % MVC intensities, respectively. Activation volume increased with a greater torque intensity [main effect of torque intensity, $F(3, 11) = 3.67$, $p = 0.020$] in a strong linear trend [$F(1, 13) = 4.01$, $p = 0.052$].

Right superior occipital gyrus—Activation volumes were $2,070 \pm 1,538$, $1,895 \pm 1,276$, $3,105 \pm 1,586$, and $2,949 \pm 1,771$ voxels at 10, 30, 50, and 70 % MVC intensities, respectively. Activation volume increased with a greater torque intensity [$F(3, 11) = 3.12$, $p = 0.037$] in a linear trend [$F(1, 13) = 4.781$, $p = 0.048$].

Right cerebellum (IV–V)—Activation volumes were $1,725 \pm 910$, $1,543 \pm 1,308$, $2,157 \pm 1,045$, and $2,580 \pm 1,032$ voxels at 10, 30, 50, and 70 % MVC intensities, respectively. Activation volume increased with a greater torque intensity [$F(3, 11) = 3.12$, $p = 0.040$] in a linear trend [$F(1, 13) = 6.64$, $p = 0.023$].

Left anterior cingulate cortex—Activation volumes were $3,363 \pm 1,432$, $1,975 \pm 1,260$, $2,471 \pm 1,186$, and $2,120 \pm 1,099$ voxels at 10, 30, 50, and 70 % MVC intensities, respectively. In contrast to other areas, the left anterior cingulate cortex showed a decrease in activation volume as torque intensity increased [main effect of torque intensity, $F(3, 11) = 6.18$, $p = 0.002$]. The decrease was linear [$F(1, 13) = 5.69$, $p = 0.033$] so that the activation volume for 30, 50, and 70 % MVC was significantly smaller than for the 10 % MVC ($p = 0.002$, $p = 0.016$, and $p = 0.013$, respectively).

Torque fluctuations and BOLD PSC

To gain insight into which areas of the brain were associated with the torque fluctuations during the submaximal contractions, we tested the association between the brain activity (BOLD signal intensity) and the magnitude of torque fluctuations, first with the SD of torque and then the CV. When all four intensities of contraction were pooled into the one analyses ($n = 56$), there were significant associations between the absolute torque fluctuations (SD) and mean PSC in several areas including the left putamen [$r(56) = 0.36$, $p = 0.007$], left calcarine gyrus [$r(56) = 0.30$, $p = 0.027$], right cerebellum [$r(56) = 0.47$, $p < 0.001$], M1/SMA (left paracentral lobule) [$r(56) = 0.45$, $p < 0.001$], left superior frontal gyrus, [$r(56) = 0.29$, $p = 0.03$], right insula [$r(56) = 0.28$, $p = 0.031$], left SMA/left middle cingulate cortex [$r(56) = 0.43$, $p = 0.001$], and left pallidum [$r(56) = 0.42$, $p = 0.001$] (Table 3). When the correlation analysis was performed at each contraction intensity ($n = 14$),

significant associations were found for the 10 % MVC in the left lingual gyrus [$r(14) = -0.607, p = 0.021$], for the 30 % MVC in the left occipital gyrus [$r(14) = 0.740, p = 0.002$], and right insula lobe [$r(14) = 0.650, p = 0.012$].

Because the SD of force covaries with intensities of contraction, the torque fluctuations were normalized to the mean torque (i.e., CV of torque) and associations with the various brain areas determined. There were significant correlations with the mean PSC in several areas including the right inferior parietal lobule [$r(56) = -0.278, p = 0.038$], right putamen [$r(56) = -0.293, p = 0.028$], left superior frontal gyrus [$r(56) = -0.331, p = 0.013$], and right insula [$r(56) = -0.330, p = 0.013$] (Table 4). When a separate correlation analysis was performed for each contraction intensity, positive correlations were found for the 10 % MVC in the right inferior parietal lobule [$r(14) = -0.721, p = 0.004$] and for the 30 % MVC in the left superior frontal gyrus [$r(14) = -0.548, p = 0.042$], left postcentral gyrus [$r(14) = -0.793, p = 0.001$], left SMA [$r(14) = -0.548, p = 0.042$], and right middle supramarginal gyrus [$r(14) = -0.672, p = 0.008$].

Discussion

This study determined those areas of the brain that were associated with lower limb force and steadiness during isometric contractions over a range of intensities in young men and women. We found that activation in the primary motor and sensory cortices, basal ganglia and cerebellum scaled linearly with increased torque of the ankle dorsiflexor muscles and similarly in men and women. A unique and important finding of this study was that several motor areas (basal ganglia, cerebellum, M1/SMA, and insula) and some typically non-motor areas (superior frontal gyrus, cingulate cortex) increased in activation as fluctuations in torque increased in higher intensity contractions. Furthermore, in order to account for the increased intensity of contraction, we determined those areas of the brain that were associated with the fluctuations in torque when normalized to the mean target torque (CV). The results indicate that the putamen, insula, contralateral superior frontal gyrus, and ipsilateral inferior lobes play an important role in control of steadiness of the lower limb during target-matching contractions. The minimal sex differences in brain activation during the steady isometric contractions explain the similar steadiness of men and women during ankle dorsiflexion; these findings also corroborate other work (Hunter et al. 2006) that indicates men and women are similarly motivated and able to activate cortical centers during maximal and submaximal performance of motor tasks.

Brain areas associated with increased contraction intensity during isometric ankle dorsiflexion

This study extended the current literature that has examined cortical activation of foot movements (Dobkin et al. 2004; MacIntosh et al. 2004; Ciccarelli et al. 2005; Huda et al. 2008; Orr et al. 2008; Francis et al. 2009) by identifying those activated areas that control for contraction intensity during an isometric task with the lower limb. The BOLD PSC increased linearly as the level of contraction intensity increased for the lower limb in several cortical and subcortical regions including contralateral primary motor cortex/SMA, putamen, and pallidum in the basal ganglia, cingulate cortex, and ipsilateral cerebellum,

with the greatest differences occurring between the 10 and 70 % MVC contraction torques. Activation volume did not increase in several of the motor regions (e.g., M1/SMA, basal ganglia) that showed greater PSC of the BOLD as contraction force increased. Typically, the central nervous system uses two strategies to increase force: recruitment of motor units and rate coding of the motor unit (Monster and Chan 1977; De Luca et al. 1982; Van Cutsem et al. 1997). For the tibialis anterior muscle, recruitment of motor units is adopted to increase force across up to ~90 % MVC (Van Cutsem et al. 1997) which is a larger recruitment range than intrinsic muscles of the hand such as the first dorsal interosseous which has a recruitment range to ~50 % MVC (De Luca et al. 1982). Our findings suggest that increased force of the tibialis anterior muscle and the recruitment of motor units are achieved by increased intensity of cortical activation in several key motor areas. These areas are addressed below.

Blood oxygenation level-dependent signal intensity in M1/SMA increased linearly with intensity of contraction. This change in BOLD signal intensity for the low and moderate contraction intensities was also observed in several fMRI studies of the hand (Spraker et al. 2007; van Duinen et al. 2008; Noble et al. 2011). Although we did not see a significant difference between 10 and 30 % MVC as was observed by Keisker et al. (2009) for dynamic power grip task, the increase was linear across the forces indicating that brain activation scaled appropriately between low and high forces to achieve greater motor unit recruitment required to increase the contraction intensity.

The basal ganglia played a significant role in the control of force of the ankle dorsiflexor muscles similar to what is shown for hand muscles (Kinoshita et al. 2000; Spraker et al. 2007). BOLD signal activity during hand contractions can vary substantially in the different nuclei of the basal ganglia according to the task requirements such as task selection and prediction, and amplitude and rate of force production (Prodoehl et al. 2009). For example, Spraker et al. (2007) found that both the globus pallidus external and the subthalamic nucleus scaled in activation intensity with increasing force amplitude; however, this was not the case for the globus pallidus internal, putamen, and caudate nucleus. Our results show a linear increase in activation intensity in the putamen with increased force with the lower limb muscles. Although we did not divide the globus pallidus into internal and external portions as others have for hand exercise (Spraker et al. 2007; Vaillancourt et al. 2007; Prodoehl et al. 2009), we showed that the globus pallidus (pallidum) had a linear increase in BOLD signal with the increase in the force level as others have shown for the hand (Vaillancourt et al. 2004, 2007; Spraker et al. 2007; Grafton and Tunik 2011).

The cerebellum scaled linearly in intensity of activation as contraction force increased, and in contrast to other motor areas, the volume of activation increased in this motor region. Others have shown increased cerebellum activation with increased hand muscle force (Kuhtz-Buschbeck et al. 2008; Keisker et al. 2009). The force-related activation in our study was mainly found in the anterior portion of the cerebellum, which is related to sensorimotor control (Manni and Petrosini 2004; Stoodley and Schmahmann 2009; 2010). We also found force-related activation in the ipsilateral anterior lobe (lobule III and IV) which is thought to be related to sensory function in detecting pain (Iadarola et al. 1998). A growing number of studies support the hypothesis that the cerebellum influences not only the sensorimotor

control of movement but also cognitive and emotional function (O'Reilly et al. 2010; Stoodley and Schmahmann 2010). Thus, the cerebellum along with other motor areas including the primary motor cortex, SMA, and basal ganglia plays a key role in modulating intensity of force of the lower limb, but the increase in activation and volume also may reflect its role in sensorimotor integration.

Appropriate visual cortical centers were activated during the motor task performance because participants were required to utilize visual feedback and trace a horizontal cursor with the target torque presented via a rear-projection visual display system. These visual areas, however, did not scale linearly with intensity of contraction. The visual areas that were activated during right ankle dorsiflexion during all tasks included the lingual gyrus, calcarine gyrus, and parietal lobule in both parietal and occipital lobes, and each of these areas is known to be active in visual processing. The lingual gyrus was likely responsible for assisting with visual recognition of the target (Gron et al. 2000), the calcarine gyrus (V1) for the central visual field and spatial attention (Martínez et al. 1999), and the parietal lobule likely contributed to the ability of participants to respond to visual sensory input with appropriate motor output (Clower et al. 2001).

Cortical areas associated with steadiness during an isometric contraction

A novel finding of this study was the identification of brain areas that control the maintenance of a steady contraction during a target-matching task with the lower limb of young adults. As expected, the amplitude of the torque fluctuations (SD of torque) increased linearly with the level of absolute contraction force (Galganski et al. 1993; Moritz et al. 2005; Tracy 2007a). Accordingly, those motor areas of the brain that increased activation intensity between low and high forces, the basal ganglia, M1, SMA, and cerebellum, were also those associated with the SD of the torque in both men and women. One exception was the positive correlation with the PSC in contralateral calcarine gyrus where the primary visual cortex is located (Rajimehr et al. 2008). Despite the linear correlation found for the visual area when all intensity conditions were pooled, the left lingual gyrus, which is also a visual area, showed a negative relation when correlation analysis was performed separately at each contraction intensity. The reduced activity of some visual areas as force increased may be related to the importance of the visual feedback in maintaining a steady contraction at the lower forces, although in young adults, the effect of visual feedback is minimal compared with other populations such as older adults (Tracy 2007b).

Because the intensity of the PSC with increased SD of torque in several motor areas covaried with the contraction intensity, we also examined the CV of torque (amplitude of the fluctuations normalized to the mean torque). The CV of torque was greatest at the lowest intensity of contraction (10 % MVC) (see Fig. 2c) for both men and women as found for several upper and lower limb muscles (Laidlaw et al. 1999; Burnett et al. 2000; Jones et al. 2002; Taylor et al. 2003; Tracy 2007b; Jesunathadas et al. 2012). Several areas, including two motor areas, the putamen and contralateral superior frontal gyrus, as well as the insula and ipsilateral inferior lobes were associated with the CV of force when all the contraction intensities were pooled. The putamen, in the basal ganglia, also showed increased PSC as contraction intensity increased (Fig. 4a). Although not found in this current study, the

activation in the left superior frontal gyrus was also large during a lower force task of the hand (Kuhtz-Buschbeck et al. 2001) and was associated with force during a power grip task (Kuhtz-Buschbeck et al. 2008). CV of force during isometric contractions is thought to be mostly mediated by low-frequency oscillations in neural drive ($<2\text{--}3\text{ Hz}$) (Negro et al. 2009; Dideriksen et al. 2012) across a range of forces. Thus, our data raise the possibility that these motor regions, the putamen and the superior frontal gyrus, are sources or significant conduits of the low-frequency oscillating neural drive that influences the trains of action potentials and ultimately the CV of force.

Both the left superior frontal gyrus motor region and the ipsilateral inferior lobes, however, showed the largest correlations between CV of force and activation for the 10 % MVC task, which is the intensity that CV was largest across the different intensities ($r = -0.55$ and -0.72 , respectively). The ipsilateral parietal lobule is typically involved in oculomotor and attention processes (Clower et al. 2001). This new finding with the lower extremity control supports previous observations that the visual processes can have a large influence on the motor variability and steadiness at the lower forces (Aagaard 2003; Sosnoff and Newell 2006; Tracy 2007b; Prodoehl and Vaillancourt 2010). Further, at low forces up to 10 %, synaptic noise and the resultant more variable motor unit discharge rates can contribute to the large CV of force (Negro et al. 2009; Dideriksen et al. 2012). Motor unit discharge rate variability, however, probably has its greatest influence on the CV at low forces in upper limb muscles and lesser effects in the tibialis anterior (Jesunathadas et al. 2012). These findings also raise the possibility that along with the superior frontal gyrus (motor region), the ipsilateral parietal lobule is also an important brain area involved in the increased CV at the lower forces during ankle dorsiflexion.

No sex differences in brain activation during ankle dorsiflexion

Although men were stronger than women, there were no differences in the normalized motor performance tasks indicating that men and women contracted their ankle dorsiflexor muscles at similar relative intensities of force and displayed similar CV and changes in force fluctuations with contraction intensity. Although there are widespread sex differences reported in the brain during cognitive and some motor tasks, we found that activation was similar for young men and women during ankle dorsiflexion for most motor areas. Only in the right inferior temporal gyrus did men display greater activation than the women during the highest contraction intensity (70 % MVC). The greater activation of temporal gyrus for men in this study is consistent with that for a finger tapping (Lissek et al. 2007). Our task was relatively simple; sex differences may become more apparent when increased task complexity and greater cognitive component are involved (Lissek et al. 2007) or for different muscle groups and postures. Our results also indicate that men and women are similarly motivated and able to activate cortical motor centers during static tasks over a range of forces.

Conclusion

Activation intensity (PSC) of several cortical and subcortical regions increased with contraction intensity during static ankle dorsiflexion including the primary motor cortex,

basal ganglia, and cerebellum. In general, activation volume did not increase in motor areas that demonstrated greater activation intensity, indicating a minimal role of volume of activation in motor unit recruitment to achieve high forces during isometric ankle dorsiflexion contractions. Activation of a visual (ipsilateral parietal lobule) and motor (contralateral superior frontal gyrus) area was associated with the greater torque fluctuations (CV) at low forces and therefore may play a role in control of steadiness especially during low-intensity contractions in young adults. Activation of the putamen (basal ganglia) was associated with both the CV of force and contraction intensity suggesting this area also plays a central role in the control of steady contractions across the range of forces. Although men were stronger than women, they had similar normalized fluctuations in torque (steadiness) when executed in the supine position and primarily similar areas and intensities of brain activation across the range of low- and high-intensity contractions. The minimal sex differences in brain activation during the steady isometric contractions indicate that young men and women are equally motivated and able to activate cortical motor centers during static tasks. Therefore, the key cortical and subcortical brain areas that were identified in healthy men and women for control of lower limb steady contractions could be targeted in future to determine impaired motor function such as occurs with aging and neurological conditions and enhanced function that can occur with physical training.

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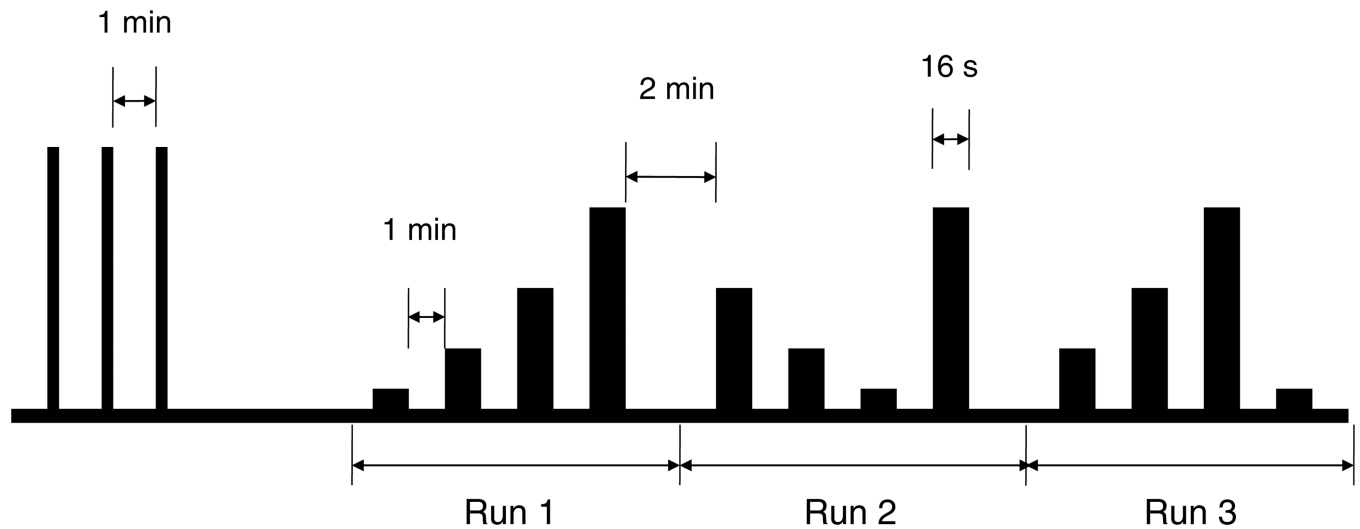
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MVC

Submaximal Contraction at 10, 30, 50 and 70% of MVC \times 3**Fig. 1.**

Experimental protocol. Three maximal voluntary contractions (MVC) of the ankle dorsiflexor muscles were performed to determine the target torque. Each subject performed three sets (runs) of isometric contractions at 10, 30, 50, and 70 % of MVC in a randomized order. Each contraction was held for 16 s followed by 60-s rest to avoid fatigue. Participants received real-time torque feedback during the contraction via a rear-projection visual display system and were required to track a horizontal target line on the display screen

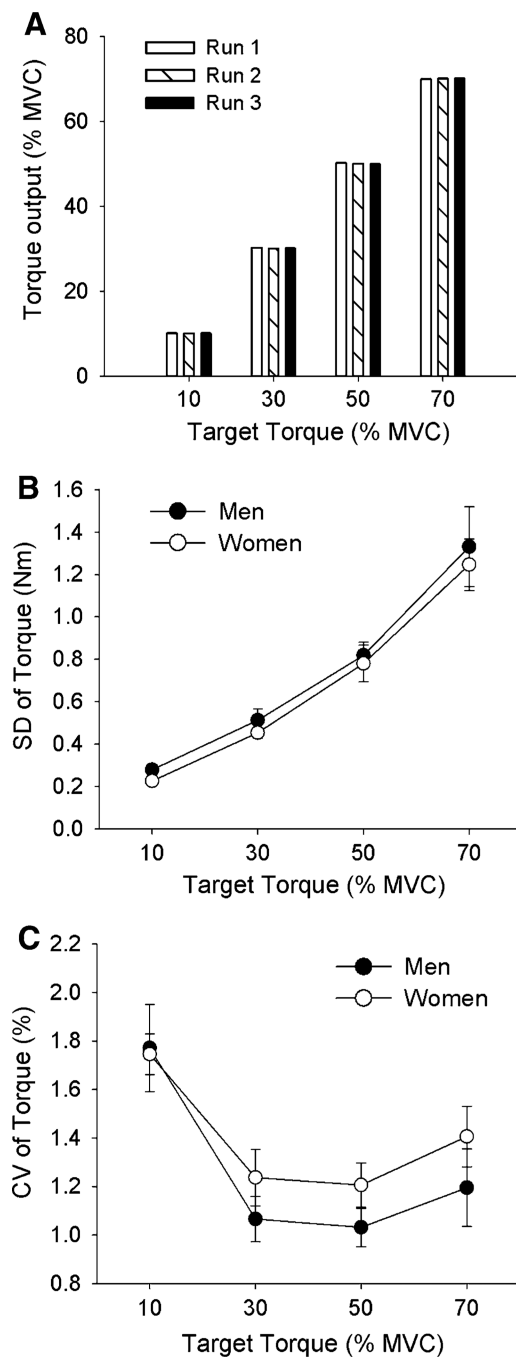


Fig. 2.

Torque and steadiness. **a** Average torque output at 10, 30, 50, and 70 % of MVC of the ankle dorsiflexor muscles. The standard errors are present in the figure but are relatively small (ranged 0.011–0.102 for 10 and 70 % conditions, respectively) compared with the mean force output. Average torque was significantly different between each target torque level ($p < 0.001$); **b** standard deviation (SD) of torque in men (*closed circle*) and women (*open circle*). The SD of torque increased as intensity of contraction increased from 10 to 70 % of MVC ($p < 0.001$); **c** coefficient of variation (CV) of torque in men (*closed circle*) and

women (*open circle*). CV at the 10 % condition was significantly greater than the other conditions ($p < 0.001$). The CV decreased and was described as a quadratic trend ($p < 0.001$). There was no difference in torque, SD of torque, and CV of torque between the three runs ($p > 0.05$), so all run data were averaged across each torque level. Shown are the means (\pm SEM)

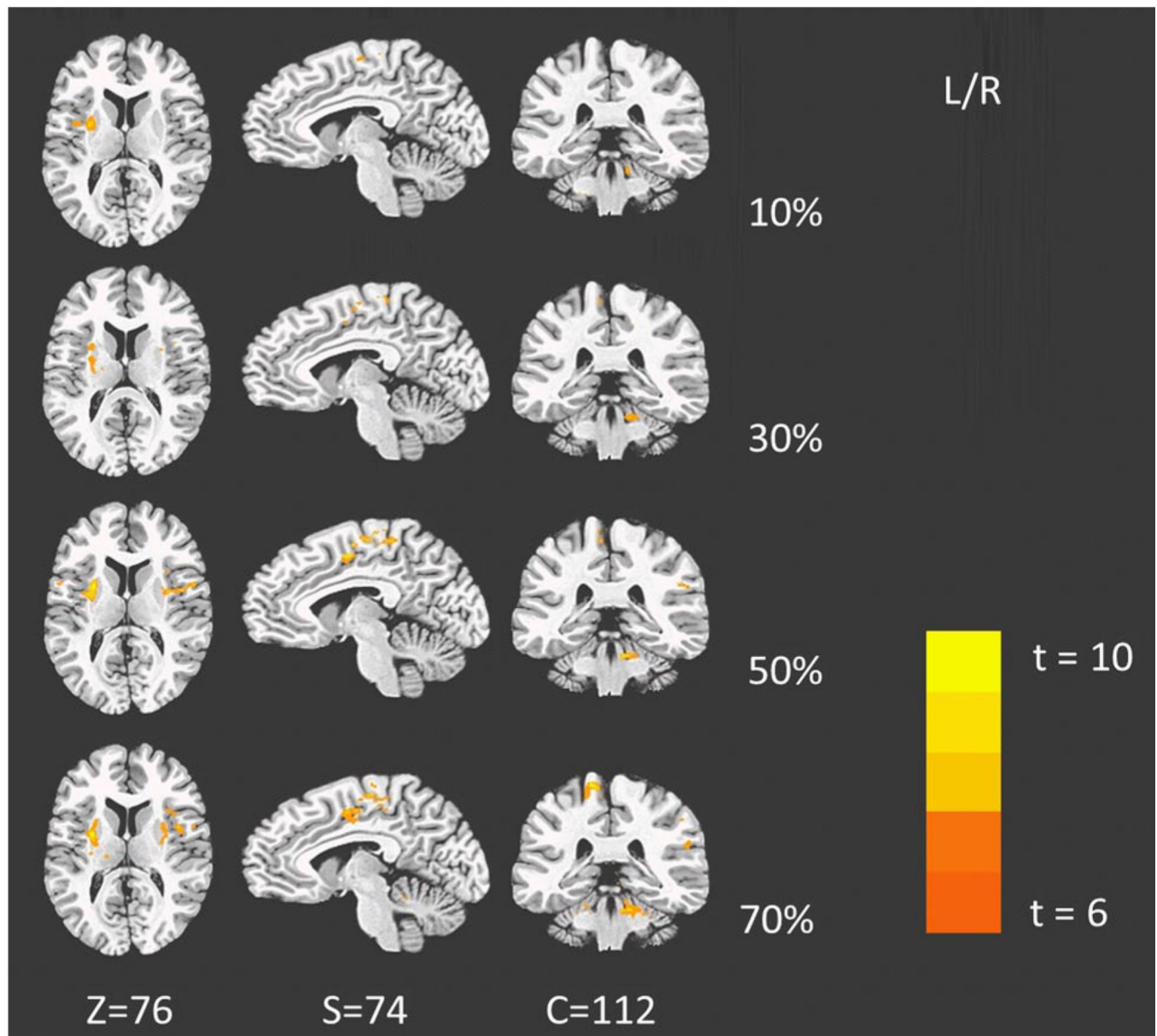
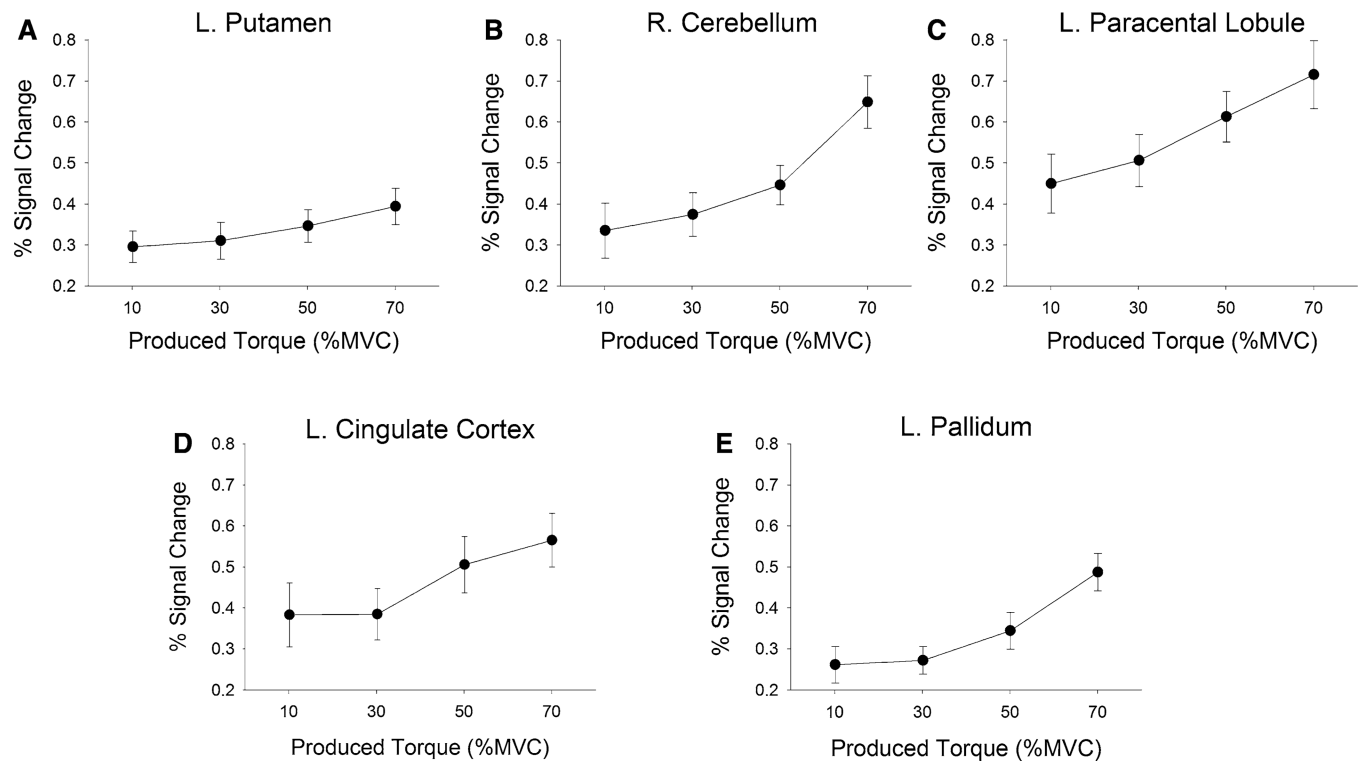


Fig. 3.

Brain activation area during right ankle isometric dorsiflexion. Activation areas were identified from contrasts between each contraction and rest. Cortical and subcortical regions activated during each contraction intensity were displayed in orange to yellow color ($t = 6$ to 10) on the same slice, i.e., on axial, sagittal, and coronal planes (76, 74, 112). The activation regions were thresholded with $p < 0.0001$ for each voxel and an activation cluster minimum of 168.8 μl so that all included voxels had a t value > 5.32 .

**Fig. 4.**

Percent signal change of regions of interest (ROI) that scaled with torque intensity. Shown are group mean (\pm SEM) of percent signal change during 10, 30, 50, and 70 % of MVC torque conditions. **a** Left putamen (effect of torque, linearity, respectively; $p = 0.028$, $p = 0.03$); **b** right cerebellum III ($p = 0.026$, $p = 0.004$); **c** left paracentral lobule ($p = 0.001$, $p = 0.01$); **d** left middle cingulate cortex ($p = 0.01$, $p = 0.025$); **e** left pallidum ($p < 0.001$, $p < 0.001$)

Table 1

Brain activation area during right ankle isometric dorsiflexion ($n = 6$ men and 8 women)

Brain regions	Cluster size (μ l)	Coordinates (mm)			Contraction versus rest		
		x	y	z	t score	z score	
L. Putamen	3,247	27	4	13	6.52	4.35	
L. Lingual gyrus	1,219	14	67	-6	6.15	4.21	
L. Calcarine gyrus	1,157	4	67	12	5.90	4.12	
R. Cerebellum (III)	1,138	-12	35	-22	6.36	4.29	
L. Paracentral lobule (M1) (5 mm from L. SMA)	800	4	15	56	6.04	4.17	
L. S. Occipital gyrus	582	11	85	4	5.92	4.12	
R. I. Parietal lobule	542	-33	44	45	6.07	4.18	
R. Putamen	484	-30	0	11	5.77	4.06	
L. S. Frontal gyrus	368	22	13	53	6.07	4.18	
R. I. Frontal gyrus	312	-49	-4	17	5.95	4.14	
L. I. Parietal lobule	312	29	46	49	5.79	4.07	
L. S. Occipital gyrus	281	17	86	20	5.75	4.05	
R. Insula lobe (Or R.I.F. G = Opercularis)	244	-41	-11	7	6.17	4.22	
R. Insula lobe	236	-39	13	15	6.31	4.27	
L. Middle cingulate cortex	232	6	4	44	5.99	4.15	
L. Pallidum (3 mm for putamen; 5 for Thalamus)	205	20	5	1	6.66	4.40	
R. I. Temporal gyrus	195	-39	60	-5	5.80	4.07	

Regions are listed accordingly to their cluster size. Coordinates are used in mm in T-T Atlas space. The activation regions were thresholded with $p < 0.0001$ and an activation cluster minimum of 168.8 μ l so that all included voxels had a t value > 5.32

R right, L left, S superior, I inferior

Table 2

Areas with increased activation volume during submaximal contractions with the right ankle isometric dorsiflexor muscles

Regions for CA_N27_ML atlas	Effect of force (<i>p</i> value)	Linear trend (<i>p</i> value)
L. Precentral gyrus (primary motor cortex, M1)	>0.05	0.029
R. Inferior frontal gyrus (p. Orbitalis)	0.02	0.052
L. Anterior cingulate cortex	0.002	0.033
L. Para hippocampal gyrus	>0.05	0.038
L. Amygdala	>0.05	0.047
R. Amygdala	>0.05	0.026
L. S. Occipital gyrus	>0.05	0.069
R. S. Occipital gyrus	0.037	0.048
R. Fusiform gyrus	>0.05	0.044
L. Postcentral gyrus	>0.05	0.059
R. Paracentral lobule	>0.05	0.083
L. Putamen	0.059	>0.05
L. Thalamus	>0.05	0.094
R. Inferior temporal gyrus	0.053	>0.05
L. Cerebellum (IV–V)	0.085	>0.05
R. Cerebellum (IV–V)	0.04	0.023
R. Cerebellum (VI)	0.059	>0.05

Areas that had significant linear increases in voxel number with increased force are shown

The activation regions were thresholded with the average PSC value of whole activation area

R right, *L* left, *S* superior, *I* inferior

Table 3

Correlation between torque fluctuations (SD) and PSC ($N = 56$; all torque conditions pooled)

	SD of force	L. Putamen	L. Calcarine gyrus	R. Cerebellum	L. M1/SMA	L. S. Frontal gyrus	R. Insula	L.M. Cingulate Cortex	L. Pallidum
SD of force	1								
L. Putamen	0.359**	1							
L. Calcarine Gyrus	0.295*	0.251	1						
R. Cerebellum	0.472**	0.613**	0.550**	1					
L. M1/SMA	0.451**	0.708**	0.582**	0.737**	1				
L. S. Frontal gyrus	0.290*	0.617**	0.530**	0.674**	0.815**	1			
R. Insula	0.277*	0.428**	0.735**	0.492**	0.700**	0.696**	1		
L. M. cingulate cortex	0.433**	0.545**	0.680**	0.668**	0.693**	0.546**	0.654**	1	
L. Pallidum	0.418**	0.426**	0.421**	0.601**	0.553**	0.479**	0.384**	0.561**	1

L left, *R* right, *S* superior, *M* middle

* $p < 0.05$,

** $p < 0.01$

Correlations between torque fluctuations (CV) and PSC ($N = 56$; all torque conditions pooled)

Table 4

	CV of torque	R. I. Parietal lobule	R. Putamen	L. S. Frontal gyrus	R. Insula
CV of torque	1				
R. I. Parietal lobule	-0.278*	1			
R. Putamen	-0.293*	0.567**	1		
L. S. Frontal gyrus	-0.331*	0.477**	0.615**	1	
R. Insula	-0.330*	0.417**	0.571**	0.444**	1

L left, R right, S superior, I inferior

* $p < 0.05$,

** $p < 0.01$